Remarks

Claims 25, 28, 31, 34, and 36 have been cancelled. Claim 26 has been amended and is believed to conform more closely to the preferred language set forth in the previous Office Action and discussed in the prior telephone interview, as discussed in the present Office Action. Claim 35 has been amended to depend from claim 26 and to clarify the fragments that fall within the scope of this claim. Claims 40 though 42 have been added.

Objections under 35 USC § 112

Claim 26 was objected to as being in improper Markush format in lacking an "and" in line 4. Claim 26 has been amended, and is believed to be in proper Markush format. Accordingly, Applicants request that the objection be withdrawn.

Rejections under 35 USC § 112, first paragraph

Claims 25 – 39 were rejected under 25 USC § 112, first paragraph, as not being enabled because the specification allegedly does not reasonably provide enablement for methods utilizing fragments or variants of NEMO and CYLD polypeptides. The Examiner asserts that it would constitute undue experimentation to practice the claimed invention due to the alleged unpredictability of knowing the degree of variance allowed or the fragment involved would still allow the NEMO and CYLD polypeptides to be biologically active. Applicants respectfully disagree, and submit that it is a matter of routine experimentation to make such fragments or variants, evaluate whether they are at least 80% identical to the native polypeptides, and determine whether they are capable of binding the other binding partner. Nevertheless, in an effort to be cooperative and speed allowance of the remaining claims, claim 25 has been canceled, and claim 26 amended to be in independent form. Support for the specific fragments set forth in claim 26 is found in the specification, at page 9, line 29 through page 10, line 9. Applicants specifically reserve the right to pursue claims directed to additional fragments and/or variants in, for example, a continuation application. The aforementioned amendment is believed to address the Examiner's rejection, accordingly, claim 26 and claims dependent thereon are believed to be allowable, and applicants respectfully request that the rejection be withdrawn.

Claims 25 – 39 were similarly rejected under 25 USC § 112, first paragraph, as containing subject matter allegedly not described in the specification in such a way as to convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention. The Examiner asserts that the only fragments or variants that meet the written description provisions of 35 USC § 112, first paragraph, are fragment 287-419 of SEQ ID

NO2 and the fragments listed on page 9, line 30 to page 10, line 9. Applicants respectfully disagree, and submit that those of ordinary skill in the art are aware of additional fragments and variants that could be prepared using routine experimentation. Moreover, to describe such variants and fragments in functional terms relating them to the polypeptides of SEQ ID NOs:2 and 4 (i.e., by using % identity or fragment language) is, Applicants believe, the most concise way of describing that which is well-known in the art.

Nevertheless, in an effort to be cooperative and speed allowance of the remaining claims, claim 25 has been canceled, and claim 26 amended to be in independent form. As the Examiner has noted, support for the specific fragments set forth in claim 26 is found in the specification, at page 9, line 29 through page 10, line 9. Applicants specifically reserve the right to pursue claims directed to additional fragments and/or variants in, for example, a continuation application. The aforementioned amendment is believed to address the Examiner's rejection, accordingly, claim 26 and claims dependent thereon are believed to be allowable, and Applicants respectfully request that the rejection be withdrawn.

The Examiner further appeared to object to the use of the transitional terms "comprising" and "consisting essentially of" in the claims, stating that the claims encompass other polypeptide sequences that do not meet the written description requirement. Applicants respectfully disagree. These terms are well-understood terms of art in the patent field. "Comprising" is an inclusive term that does not exclude additional elements or method steps not recited in the claim. See, e.g., *Genentech, Inc. v. Chiron Corp.*, 112 F.3d 495, 501, 42 USPQ2d 1608, 1613 (Fed. Cir. 1997). ("Comprising" is a term of art used in claim language which means that the named elements are essential, but other elements may be added and still form a construct within the scope of the claim.). The phrase "consisting essentially of has a long-understood meaning in patent claims to encompass the specified materials or steps "and those that do not materially affect the basic and novel characteristic(s)" of the claimed invention. *In re Herz*, 537 F.2d 549, 551-52, 190 USPQ 461, 463 (CCPA 1976) (emphasis in original). Those of ordinary skill in the art are aware of numerous polypeptide sequences that could be added to the NEMO and/or CYLD polypeptides.

If the concern is that the use of the term "comprising" encompasses NEMO and/or CYLD polypeptides to which have been added other polypeptide sequences that adversely affect the ability of NEMO and CYLD to bind each other, Applicants respectfully note that the claims state that the NEMO and CYLD polypeptides are capable of binding each other. This claim element is not a narrowing element, inasmuch as those of skill in the art would not use a NEMO or CYLD polypeptide that was not capable of binding the respective binding partner in a method for determining the effect of a compound on their binding. Applicants respectfully submit that such language is not necessary in claims using the transitional phrase "consisting essentially of"

because it is implicit that nothing that materially affects the ability of NEMO and CYLD to bind each other can be added to either polypeptide.

The present situation is analogous to Example 8 in the Written Description guidelines (http://www.uspto.gov/web/menu/written.pdf), in which a claim to an isolated and purifed nucleic acid comprising a specific SEQ ID NO meets the written description requirement: a review of the specification reveals that the NEMO and CYLD polypeptides and fragments thereof are essential to the operation and function of the claimed invention, and a review of the claims indicates that they are drawn to a method using a genus of NEMO polypeptides (i.e., any NEMO polypeptides that at a minimum contain the smallest functional fragment of NEMO) and a genus of CYLD polypeptides (i.e., any CYLD polypeptides that at a minimum contain the smallest functional fragment of CYLD). One of skill in the art can readily envision polypeptides that include the NEMO (or CYLD) polypeptide set forth because such polypeptides are routinely expressed as part of a larger polypeptide.

For example, recombinant polypeptides are often expressed with the addition of a signal peptide. Such signal peptides can facilitate isolation of the recombinant polypeptide since they are secreted into culture medium, from which they may be more easily purified than if they were retained within the host cell. Recombinant polypeptides can also be expressed as fusion proteins, as discussed in a section from Molecular Cloning: A Laboratory Manual, 3rd Edition (Sambrook and Russell, eds; Cold Spring Harbor Laboratory Press, 2001; submitted herewith as Exhibit A). This manual is a well-known, widely referenced manual in the art of molecular biology; the enclosed section discusses fusion proteins in the context of epitope tagging. After briefly describing fusion proteins (paragraph one of the Overview), it is noted that an epitope tag should not affect the function of the protein (second paragraph of the overview). Several peptides that have been used for epitope tags are shown in Table 17-3 (tag polypeptides are peptides that facilitate detection and/or purification of a recombinant protein). Thus, those of skill in the art at the time the application was file were aware of various tag peptides, and considered production of such fusion proteins to be routine.

Furthermore, Applicants have disclosed a number of tag polypeptides on page 10, line 29, through page 11, line 12 and discussed what those of skill in the art knew about fusion polypeptides in there previous response. Applicants respectfully submit that that the description in the specification together with the knowledge routinely available to one of ordinary skill in the art conveys to those of ordinary skill in the art that Applicants were in possession of the claimed method, utilizing a genus of NEMO polypeptides and a genus of CYLD polypeptides. To limit Applicants claims to methods utilizing polypeptides "consisting of" specific amino acid sequences would unfairly penalize them for fully disclosing their invention. A potential infringer

could avoid literal infringement of the claims by simply adding a single amino acid to the carboxy or amino terminus of either of the two peptides. Accordingly, Applicants request that this aspect of the rejection be withdrawn.

Rejections under 35 USC § 112, second paragraph

Claims 25 – 39 were rejected under 25 USC § 112, second paragraph, as allegedly being vague and indefinite in the use of the abbreviations "NfkappaB" and "CD40." Applicants respectfully disagree; these abbreviations are well known by those of skill in the art. For example, a search of the USPTO database of patents issued since 1976 having the term "CD40" in the claims and the term "protein" anywhere in the patent yielded 101 issued US patents, and a search for "NF-kappaB" or "NF-kappa-B" in the claims yielded five issued patents. Moreover, claim 25 has been canceled, and the rejection thereof is thus moot. Nevertheless, in an effort to be cooperative and speed allowance of the claims, Applicants have spelled out the full name of the NfkappaB, as suggested by the Examiner. The claims as amended no longer use the allegedly indefinite term "CD40." This amendment does not alter the scope of the claims, and is believed to address the Examiner's rejection; accordingly, applicants request that the rejection be withdrawn.

Claims 25 and 34 were rejected under 25 USC § 112, second paragraph, as allegedly vague and indefinite in the use of the phrase "inhibition of binding...by at least 50%." According to the Examiner, it is unclear whether the claim is referring to 50% of the surface of the molecules being bound, 50% of trial cases testing inhibition, or other allegedly countless scenarios. Applicants respectfully assert that those of ordinary skill in the art readily understand what is meant by a 50% inhibition in binding; nevertheless, in an effort to be cooperative and speed allowance of the claims, Applicants have amended claim 26 to recite wherein when the amount of binding of the NEMO polypeptide to the CYLD polypeptide in the presence of the test compound is less than about 50 % of the binding of the NEMO polypeptide to the CYLD polypeptide in the absence of the test compound, the test compound inhibits the binding of NEMO and CYLD. Claims 25 and 34 have been cancelled; the amendment is believed to address the rejection, and accordingly Applicants request that it be withdrawn.

CONCLUSIONS

Claims 26 – 27, 29 – 30, 32 – 33, 35 and 37 -42 are now pending in the application and are believed to be in condition for allowance. Applicants have incorporated language suggested by the Examiner, to speed prosecution and allowance of the claims. The amendments or changes in phraseology made herein are made solely in an effort to speed allowance of the claims. Accordingly, Applicants respectfully assert their rights to pursue any subject matter that may have been excluded by their amendments (as in a continuation application or equivalent), and to pursue all remedies available against potential infringers, including use of the doctrine of equivalents. If the examiner has any questions or concerns about the present claims, she is asked to contact the undersigned at the direct dial number given below, to facilitate prosecution and speed allowance of the claims.

Respectfully submitted,

Patricia Anne Perkins
Agent for Applicants
Registration No. 34,693
DIRECT DIAL (206)265-4782
Date: November 7, 2003

Law Department

Immunex Corporation
51 University Street
Seattle, WA 98101

Attach: Exhibit A

EXHIBIT A

Molecular Cloning

A LABORATORY MANUAL

THIRD EDITION

Front cover (paperback): The gene encoding green fluorescent protein was cloned from *Aequorea victoria*, a jellyfish found in abundance in Puget Sound, Washington State. This picture of a 50-mm medusa was taken on color film by flash photography and shows light reflected from various morphological features of the animal. The small bright roundish blobs in the photograph are symbiotic amphipods living on or in the medusa. The bright ragged area in the center is the jellyfish's mouth.

Bioluminescence from *Aequorea* is emitted only from the margins of the medusae and cannot be seen in this image. Bioluminescence of *Aequorea*, as in most species of jellyfish, does not look like a soft overall glow, but occurs only at the rim of the bell and, given the right viewing conditions, would appear as a string of nearly microscopic fusiform green lights. The primary luminescence produced by *Aequorea* is actually bluish in color and is emitted by the protein aequorin. In a living jellyfish, light is emitted via the coupled green fluorescent protein, which causes the luminescence to appear green to the observer.

The figure and legend were kindly provided by Claudia Mills of the University of Washington, Friday Harbor. For further information, please see Mills, C.E. 1999–2000. Bioluminescence of *Aequorea*, a hydromedusa. Electronic Internet document available at http://faculty.washington.edu/cemills/Aequorea.html. Published by the author, web page established June 1999, last updated 23 August 2000.

Back cover (paperback): A portion of a human cDNA array hybridized with a red fluor-tagged experimental sample and a green fluor-tagged reference sample. Please see Appendix 10 for details. (Image provided by Vivek Mittal and Michael Wigler, Cold Spring Harbor Laboratory.)

Library of Congress Cataloging-in-Publication Data

Sambrook, Joseph.
Molecular cloning : a laboratory manual / Joseph Sambrook, David W. Russell.-- 3rd ed.
p. ; cm.
Includes bibliographical references and index.
ISBN 0-87969-576-5 (cloth) -- ISBN 0-87969-577-3 (pbk)
1. Molecular cloning--Laboratory manuals.
[DNLM: 1. Cloning, Molecular--Laboratory Manuals. QH 440.5 S187m 2001] I. Russell, David W. (David William), 1954- . II. Title.
QH442.2 .S26 2001
572.8--dc21

00-064380

10 9 8 7 6 5 4 3 2 1

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EPITOPE TAGGING

Epitope Tagging: An Overview

Fusion proteins consist of the amino acid residues of interest covalently attached at their amino or carboxyl termini to a set of carrier sequences. When the carrier sequences contain a useful antigenic determinant, the fusion protein is said to be tagged with an epitope. Epitope tagging is a powerful technique to characterize proteins of interest without purification. Another major advantage of epitope tagging is that well-characterized and highly specific antibodies can be used to study proteins of interest without the long laborious routines and uncertainties for production and characterization of antibodies. Epitope tagging has become a routine practice in the yeasts *Saccharomyces cerevisiae* and *Schizosaccharomyces pombe* (Bahler et al. 1998; Longtine et al. 1998). A tag can be fused to the carboxyl terminus of a protein at its endogenous locus using existing PCR modules without cloning and disrupting its endogenous promoter. In mammalian cells, this approach is not feasible at the present time. In most cases, the fusion protein is expressed under the control of a heterologous promoter (Sells and Chernoff 1995; Chubet and Brizzard 1996; Georgiev et al. 1996; Hosfield and Lu 1998), which typically results in abnormal expression of the gene of interest. Therefore, epitope tagging cannot be used, for example, to study regulation of a cell-cycle-regulated gene.

One assumption here is that addition of an epitope tag does not affect the function, intracellular transport, modification, or location of the target protein. Several studies have suggested that most proteins can accept a tag at one terminus or other regions without severe loss of their functions (Prasad and Goff 1989; Anand et al. 1993; Ross-Macdonald et al. 1997). However, whether this holds true must be tested whenever possible. In yeast, where the excavation of chromosomal genes is a routine matter, it is often possible to erase any doubts immediately by testing the ability of the epitope-tagged protein to complement a null allele. In mammalian cells, these matters must be taken on faith, and any results obtained should remain open to question until they have been confirmed by other means. In cases where a sensitive functional assay is available in vitro, it is sometimes possible to synthesize enough of the tagged protein in cell-free systems to confirm that it has retained full activity.

Epitope Tagging: Practical Considerations

Table 17-3 presents a sample of the epitopes that have been used for tagging. Because most of these epitopes are derived from a hormone or an oncogene, there is a finite but small chance of immunological cross-reaction with cellular material. In most cases, a single monoclonal antibody specific for the epitope can be used for immunostaining, immunoblotting, immunoprecipitation, and immunopurification.

The number of well-characterized epitopes is growing rapidly, and many commercial companies now sell kits that contain the materials and instructions to construct and test epitope-tagged fusion proteins of various sorts. However, before deciding to use an epitope-tagging strategy, it is best to work out the cost of the necessary reagents. This is especially important if the goal is to use the epitope for large-scale affinity purification of the fusion protein. Some of the companies charge such outrageous prices for monoclonal antibodies that the ongoing cost of the system quickly becomes prohibitive for many laboratories.

Another important consideration is to determine whether the selected epitope has been used in the literature for a purpose similar to that of its intended application. Even though epitope tagging may vary from protein to protein, the fact that similar approaches have been exploited with a particular tag increases the likelihood of its success and may provide some ideas and some detailed information on how to utilize this epitope, which may not exist in most general protocols.

It is very important to choose a tag whose cognate antibody will not cross-react with a protein in the host cells used for expression of the epitope-tagged protein and to choose a tagging site on the target protein that will not interfere with the function of any topogenic sequences (e.g., hydrophobic signal sequences) or trafficking signals (e.g., nuclear transport signals or endoplasmic reticulum retention sequences). Whenever possible, however, the epitope tags should be added to the amino or the carboxyl terminus of the target protein, where they are most likely to be accessible to antibody and least likely to interfere with the function of the target protein.

When an epitope tag is used for immunopurification, it is best to choose a tag that may be removed from the target protein. Removal is sometimes necessary to restore protein function, to increase solubility,

or to decrease antigenicity. Although success is not guaranteed, removal may be accomplished by incorporating a protease cleavage site in the peptide linker between the epitope tag and the target protein (for details, please see the introduction to Chapter 15). However, enzymatic removal is often inefficient (because the cleavage site is inaccessible) and sometimes destructive (because the cleaving protease is not absolutely specific or because of contamination with nonspecific proteases) (Nagai and Thøgersen 1987; Dykes et al. 1988).

Epitope Tagging: Applications

Since the introduction of epitope tagging by Munro and Pelham (1984), it has been used to address several experimental problems, including the detection, localization, and purification of expressed proteins. The protein of interest can be detected with immunological reagents directed against the epitope and purified by affinity chromotography in the absence of a functional assay (Field et al. 1988). In addition, because the tagged protein can be differentiated unambiguously from related cellular proteins (Davis and Fink 1990), its size and location can be ascertained by western blotting and immunofluorescence (Munro and Pelham 1986, 1987; Geli et al. 1988; Pelham et al. 1988; Swanson et al. 1991), its pattern of biosynthesis and post-translational modification can be followed by pulse-labeling and immunoprecipitation, and its interactions with other proteins can be probed by coimmunoprecipitation (Kolodziej and Young 1989; Squinto et al. 1990). Finally, with the development of sensitive mass spectrometry for peptide sequencing, epitope tagging has been used increasingly for purification of protein complexes and identification of components in the protein complexes (Ogryzko et al. 1998; Shao et al. 1999). Although it is not possible to provide a comprehensive list of the relevant literature, below are some recent major applications of epitope tagging.

- ***Gene expression and localization.*** Epitope tagging has been used to study gene expression in various organisms using western blotting. If it is difficult to detect the expression of a fusion protein using a single epitope, due to a low expression level and instability of the protein, sensitivity can be increased by adding multiple epitopes (Nakajima and Yaoita 1997). Once a fusion protein is expressed, its localization can be detected by immunofluorescence. This technique is very useful to study localizations of isoforms of a gene family that share highly significant sequence identity, where specific antibodies to different isoforms are always difficult to generate (Scherer et al. 1995; Toyota et al. 1998). Epitope tagging can also be used for mapping regions of a protein that are responsible for targeting the protein to specific locations (Xu et al. 1998).
- ***Interactions.*** By using coimmunoprecipitation and detection by western blotting, epitope tagging has been used widely to study protein-protein interactions in vitro and in vivo (Chinnaiyan et al. 1995; Hsu et al. 1996) (for details, please see Chapter 18, Protocols 2, 3, and 4). In cases where no antibodies are available for either of the two potentially interacting proteins, different tags may be attached to each of the two proteins. The antibody that recognizes one epitope is then used for immunoprecipitation, whereas the antibody against the other epitope is used for detection of the immunoprecipitated proteins. In this case, it is always wise to perform the reciprocal coimmunoprecipitation experiment to determine whether the interaction is specific. Morover, it is important to recognize that because candidate proteins identified by immunoprecipitation may not interact directly with the bait protein, it is advisable to use other means to confirm whether a direct interaction exists.
- ***Purification of protein complexes.*** In many cases, a biological function is carried out by a protein complex instead of a single protein. Therefore, it is essential to identify and purify all of the components of a protein complex. In organisms such as yeast where genetic approaches exist to identify all of the components performing the same function, it is still necessary to purify protein complexes to study their biochemical functions. Epitope tagging has provided a way to purify protein complexes by immunoaffinity chromatography and immunoprecipitation (Chiang and Roeder 1993; Ogryzko et al. 1998; Shao et al. 1999). Now that the complete genomic sequences of several organisms are available (e.g., the yeast *S. cerevisiae, C. elegans*, and *Drosophila*), and with the significant reduction in the amounts of materials required for peptide sequencing by mass spectrometry (Dukan et al. 1998; Huang et al. 2000), the use of immunoprecipitation to identify components in protein complexes is likely to become one of the major techniques in proteomics.

TABLE 17-3 Epitope Tagging

Origin of Tag	Description of Epitope	Source of Antibodies	References
Substance P	QFFGLM The sequence of this hexapeptide corresponds to the carboxy-terminal half of substance P.	MAb NCI/34 to substance P recognizes only the carboxy-terminal pentapeptide of substance P (Cuello et al. 1979). However, this antibody can be used for western blotting or immunofluorescence only after carboxyl groups in the target protein have been converted to amides with soluble carbodiimide and NH_4Cl (Munro and Pelham 1984).	Cuello et al. (1979); Munro and Pelham (1984); Albers and Fuchs (1987)
Human c-Myc protein	EQKLISEEDL	MAb 9E10 (Evan et al. 1985) was raised against a synthetic peptide comprising residues 409–439 of human c-*myc*. The epitope recognized by MAb 9E10 was identified by progressive deletion of residues 409–439 of c-*myc* (Munro and Pelham 1986).	Evan et al. (1985); Munro and Pelham (1986, 1987); Pelham et al. (1988); Squinto et al. (1990); Adamson et al. (1992); Sells and Chernoff (1995)
Anonymous open reading frame	KAEDESS The translational stop codon at the end of the *HGPRT* gene was mutated to allow extended translation to the next in-frame stop codon. The resulting protein, which is enzymatically active, carries a unique negatively charged heptapeptide at its carboxyl terminus.	Polyclonal antibodies were raised against a synthetic peptide and affinity-purified.	Yee et al. (1987)
Colicin A protein	178 amino-terminal amino acids of colicin A protein.	MAb 1c11 recognizes an epitope located in the first 70 amino acids of colicin A protein (Cavard et al. 1986).	Cavard et al. (1986)
Influenza virus hemagglutinin	YPYDVPDYA	MAbs were originally raised against a synthetic peptide corresponding to amino acids 75–110 of the hemagglutinin protein of the H3 subtype of influenza virus (Niman et al. 1983). MAbs 12CA5 and 3F10 are now available commercially from Berkeley Antibody Co. (Babco), which recognize the complete antigenic determinant (YPYDVPDYA) of the immunizing 36-residue peptide (Wilson et al. 1984). This nonapeptide can be used to release fusion proteins from the MAb.	Niman et al. (1983); Wilson et al. (1984); Field et al. (1988); Swanson et al. (1991); West et al. (1992); Marck et al. (1993); Sells and Chernoff (1995)
SV40 T antigen	85 amino-terminal amino acids of SV40 large T antigen.	MAb Pab 419 (L19 in Harlow et al. 1981).	Harlow et al. (1981); Sugano et al. (1992)
FLAG sequence	DYKDDDDK FLAG was designed as a hydrophilic, immunogenic purification tag that could be removed from the target protein by proteolytic cleavage (Hopp et al. 1988). The five carboxy-terminal amino acids of the FLAG epitope are adapted from the site cleaved by enterokinase in its natural substrate bovine	MAb 4E11 (Hopp et al. 1988; Prickett et al. 1989), which is specific for the FLAG sequence, can be used for immunoblotting, immunoprecipitation, and immunoaffinity purification. Binding of proteins tagged with the FLAG epitope to this antibody is calcium-dependent and reversible with chelating agents such as EGTA or at low pH.	Davie and Neurath (1955); Hopp et al. (1988); Knott et al. (1988); Prickett et al. (1989)

	trypsinogen. Digestion with enterokinase, which cleaves after the lysine residue in the sequence VDDDDK (Davie and Neurath 1955), should remove an amino-terminal FLAG sequence after immunopurification of a tagged protein.		
Vesicular stomatitis virus (VSV) G protein	YTDIEMNRLGK 11 amino acids from the carboxyl terminus of VSV G protein (Kreis 1986).	Polyclonal and monoclonal antibodies were raised against a synthetic peptide containing the 15 carboxy-terminal amino acids (497–511) of VSV G protein (Kreis 1986). Affinity-purified polyclonal antibodies recognize epitopes distributed along the entire 15-residue peptide, whereas the MAb PD54 reacted only with the carboxy-terminal pentapeptide. Both types of antibodies recognize proteins tagged with the 11-residue epitope, although the polyclonal antibody reacts more strongly (Soldati and Perriard 1991).	Kreis (1986); Soldati and Perriard (1991)
T7-Tag	MASMTGGQQMG	MAb T7 • Tag (sold by Novagen).	Lutz-Freyermuth et al. (1990); Tsai et al. (1992)
AU epitopes	DTYRYI (AU1) and TDFYLK (AU5)	MAbs AU1 and AU5 were developed against papillomavirus major capsid protein.	Lim et al. (1990)
His-6 epitope	HHHHHH	MAbs 6-His, 6xHis, and HIS-11 are commercially available.	
HPOL	HPOL	Mab1051c recognizes a peptide from the thumb region of the herpes simplex virus type-1 DNA polymerase (HPOL).	Schreiner et al. (1999)
Btag	QYPALT	Two MAbs (D11 and F10) developed against the major core protein, VP7, of bluetongue virus were tested to recognize the BTag epitope at any regions of recombinant proteins.	Wang et al. (1996)
3B3	QRQYGDVFKGD	MAb 3B3 was raised against ORF gE of a varicella zoster virus and tested to react with the 3B3 epitope placed in other proteins.	Hatfield et al. (1997)
Glu-Glu	EYMPME or EFMPME	Synthetic peptide EEEEYMPME from polyomavirus medium T antigen was used to produce MAb Glu-Glu. This antibody has been used for affinity purification.	Grussenmeyer et al. (1985)
IRS	RYIRS	MAb IRS1 recognizes fusion proteins containing the epitope at the carboxyl terminus of the proteins only.	Liang et al. (1996); Luo et al. (1996)